529 Rec'd PCT/PTO 15 MAY 2000

Form PTO-1390 (Rev. 5-93) US DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NO. H 3185 PCT/US

U.S. APPLICATION NO. (If known, see 37 CFR 1.5) 09/554387

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP98/07059	November 5, 1998	November 14, 1997

TITLE OF INVENTION

USE OF MIXTURES OF ACTIVE AGENTS CONTAINING PHYTOSTENOL FOR PRODUCING HYPOCHOLESTERAEMIC PREPARATIONS

APPLICANT(S) FOR DO/EO/US

Bernd Fabry

Applicant herewith submits to the United States Designated/Elected Office (EO/DO/US) the following items and other information:

1. ■ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. □ This a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. □ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39 (1).
4. ■ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ■ A copy of the International Application as filed (35 U.S. C. 371(c)(2)).
   a. □ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ■ has been transmitted by the International Bureau.
   c. □ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ■ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ■ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. □ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. □ have been transmitted by the International Bureau.
   c. □ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ■ have not been made and will not be made.
8. □ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ■ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). **(UNEXECUTED)**
10. □ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. □ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. □ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ■ A FIRST preliminary amendment
    □ A SECOND or SUBSEQUENT preliminary amendment.
14. □ A substitute specification.
15. □ A change of power of attorney and/or address letter.
16. □ Other items or information.:

"Express Mail Post Office to Addressee" service Mailing Label Number EL541612068US .

U.S. Application No. (If known see CFR1.30)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/554387	PCT/EP98/07059	H 3185 PCT/US

17.		CALCULATIONS	PTO USE ONLY
■	The following fees are submitted: **Basic National Fee (37 CFR 1.492(a)(1)-(5)):** Search Report has been prepared by the EPO or JPO..... **$840.00**		
	International preliminary examination fee paid to USPTO (37CFR 1.482) **$670.00**		
	No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37CFR 1.445(a)(2))..... **$690.00**		
	Neither international preliminary examination fee (37CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO..... **$970.00**		
	International preliminary examination fee paid to USPTO (37CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4)..... **$96.00**		
	ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 840	00
	Surcharge of **$130.00** for furnishing the oath or declaration later than □ 20 □ 30 months from the earliest claimed priority date 37 (CFR 1.492(e)).	$ 0	00

	Claims	Number filed	Number Extra	Rate		
	Total Claims	20 - 20 =	0	0 X $18.00	$ 0	00
	Independent Claims	2 - 3 =	0	0 X $78.00	$ 0	00
	Multiple dependent claims (s)(if applicable)		0	+ $260.00	$ 0	00
	TOTAL OF ABOVE CALCULATIONS =				$ 840	00
	Reduction by ½ for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				$ 0	00
	SUBTOTAL =				$ 840	00
	Processing fee of **$130.00** for furnishing the English translation later the □ 20 □ 30 months from the earliest claimed priority date (37CFR 1.492(f)). +				$ 0	00
	TOTAL NATIONAL FEE =				$ 840	00
	Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property +				$ 0	00
	TOTAL FEES ENCLOSED =				$ 840	00
					Amount to be: refunded	$
					charged	$840.00

a. □ A check in the amount of $_____ to cover the above fees is enclosed.
b. ■ Please charge my Deposit Account No. 50-1177 in the amount of $840.00 to cover the above fees.
A triplicate copy of this sheet is enclosed. Order No. 00-0244 .
c. ■ The Assistant Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 50-1177 . A triplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO: Cognis Corporation, Law Dept.
2500 Renaissance Blvd, Suite 200
Gulph Mills, PA 19406

SIGNATURE

Aaron R. Ettelman
NAME ATTORNEY FOR APPLICANT
42,516
REGISTRATION NUMBER

Form PTO 1390 (REV 5-93)

Express Mail" Mailing Label No. EL541612275US .

PATENT
Docket No. H 3185 PCT/US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Application of
Bernd Fabry

Serial No. 09/554,387 Examiner:
Filed: 06/29/00 Art Unit:
PCT/EP98/07059
International Filing Date: November 5, 1998
Priority Date Claimed: November 14, 1997
TITLE: USE OF MIXTURES OF ACTIVE AGENTS CONTAINING PHYTOSTENOL FOR PRODUCING HYPOCHOLESTERAEMIC PREPARATIONS

TRANSMITTAL OF DECLARATION UNDER 37 CFR SECTION 1.494/5(c)

Commissioner for Patents
Box PCT
Washington, D.C. 20231

Attn: Shakeel Ahmed
DO/EO/US

Sir:

No original declaration or oath was filed earlier herein. Accordingly, enclosed is the original declaration or oath for this application.

Please charge our **Deposit Account No. 50-1177** in the amount of **$130.00** as prescribed by 37 CFR 1.492(e) for the surcharge and processing fee for filing a declaration on a date later than 20/30 months after the priority date of the application. A triplicate of this sheet is enclosed along with an executed declaration. **Order No. 00-0386.** Authorization is also granted to charge any deficiency to Deposit Account 50-1177.

07/17/2000 AGIZAW 00000103 501177 09554387
01 FC:154 130.00 CH

June 29, 2000
(Date)

Respectfully submitted,

Aaron R. Ettelman
(Reg. No. 42,516)
Attorney for Applicant
(610) 278-4930

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Gulph Mills, PA 19406

ARE/ras

"Express Mail" mailing label number EL541612068US .

PATENT
Docket No. H 3185 PCT/US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

RE: PCT/EP98/07059
International Filing Date: November 5, 1998
Priority Date Claimed: November 14, 1997
Applicant: Bernd Fabry
Title: USE OF MIXTURES OF ACTIVE AGENTS CONTAINING PHYTOSTENOL FOR PRODUCING HYPOCHOLESTERAEMIC PREPARATIONS
Applicants' Reference: H 3185 PCT/US

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Box PCT
Washington, DC 20231

ATTN: DO/EO/US

Prior to the calculation of fees and examination of the above-identified national stage application pursuant to the accompanying submission under 35 U.S.C. §371, please amend the English translation of the International Application submitted herewith, without prejudice, as follows:

In the Specification:

Please amend the instant Specification, without prejudice, as follows:

At page 1, please delete all text above line 14, including the heading "Prior Art", and insert therefor the following:

--TITLE OF THE INVENTION

Hypocholesteremic Preparations Containing
Mixtures of Phytostenol(ester)s and Conjugated Fatty Acids,
and Methods of Reducing Serum Cholesterol Levels Using the Same

Preliminary Amendment of U.S. National Stage for International Application PCT/EP98/07059 filed November 5, 1998

BACKGROUND OF THE INVENTION--

At page 2, line 16 thereof, delete "Description of the Invention" and insert therefor:

--BRIEF SUMMARY OF THE INVENTION

The present invention includes hypocholesteremic preparations comprising synergistic mixtures of phytostenols and/or phytostenol esters and conjugated fatty acids, and methods of reducing serum cholesterol levels in mammals through administration of such preparations.--

At page 2, line 32 thereof, insert:

--DETAILED DESCRIPTION OF THE INVENTION--

At page 7, line 35 thereof, delete "Commercial applicability".

Please add new page 12, which is attached hereto, containing an Abstract of the Disclosure, following the claims.

In the Claims:

Please add new claims 11-30, as follow:

--11. (New) A method of reducing serum cholesterol content in a mammal, said method comprising:

(i) providing a hypocholesteremic preparation comprising at least one component (a) selected from the group consisting of phytostenols and phytostenol esters and at least one component (b) selected from conjugated fatty acids having from about 6 to about 24 carbon atoms and glycerides of conjugated fatty acids having from about 6 to about 24 carbon atoms; and

(ii) administering the hypocholesteremic preparation to a mammal in an amount effective to reduce serum cholesterol content in the mammal.--

--12. (New) The method according to claim 11, wherein the at least one component (a) is selected from the group consisting of β-sitostenol, β-sitostanol, and esters thereof.--

--13. (New) The method according to claim 11, wherein the at least one component (a) comprises a carboxylic acid ester of a phytostenol, the carboxylic acid being of the general formula (I):

$$R^1CO\text{-}OH \qquad (I)$$

wherein R^1CO represents an acyl radical having from about 2 to about 22 carbon atoms and up to about 3 carbon-carbon double bonds.--

--14. (New) The method according to claim 12, wherein the at least one component (a) comprises a carboxylic acid ester of β-sitostenol or β-sitostanol, the carboxylic acid being of the general formula (I):

$$R^1CO\text{-}OH \qquad (I)$$

wherein R^1CO represents an acyl radical having from about 2 to about 22 carbon atoms and up to about 3 carbon-carbon double bonds.--

--15. (New) The method according to claim 13, wherein the carboxylic acid has from about 12 to about 18 carbon atoms.--

--16. (New) The method according to claim 14, wherein the carboxylic acid has from about 12 to about 18 carbon atoms.--

--17. (New) The method according to claim 11, wherein the at least one

component (b) comprises conjugated linoleic acid.--

--18. (New) The method according to claim 11, wherein the hypocholesteremic preparation is encapsulated in gelatin, whereby a gelatin capsule is provided, prior to administering the preparation to the mammal.--

--19. (New) The method according to claim 18, wherein the at least one component (a) and the at least one component (b) are each independently present in an amount of from about 0.1 to about 50% by weight, based on the total weight of the gelatin capsule.--

--20. (New) The method according to claim 11, wherein the hypocholesteremic preparation is combined with a foodstuff prior to administering the preparation to the mammal.--

--21. (New) A hypocholesteremic preparation comprising at least one component (a) selected from the group consisting of phytostenols and phytostenol esters and at least one component (b) selected from conjugated fatty acids having from about 6 to about 24 carbon atoms and glycerides of conjugated fatty acids having from about 6 to about 24 carbon atoms.--

--22. (New) The hypocholesteremic preparation according to claim 21, wherein the at least one component (a) is selected from the group consisting of β-sitostenol, β-sitostanol, and esters thereof.--

--23. (New) The hypocholesteremic preparation according to claim 21, wherein the at least one component (a) comprises a carboxylic acid ester of a phytostenol, the carboxylic acid being of the general formula (I):

$R^1CO\text{-}OH$ (I)

wherein R^1CO represents an acyl radical having from about 2 to about 22 carbon atoms and up to about 3 carbon-carbon double bonds.--

--24. (New) The hypocholesteremic preparation according to claim 22, wherein the at least one component (a) comprises a carboxylic acid ester of β-sitostenol or β-sitostanol, the carboxylic acid being of the general formula (I):

$R^1CO\text{-}OH$ (I)

wherein R^1CO represents an acyl radical having from about 2 to about 22 carbon atoms and up to about 3 carbon-carbon double bonds.--

--25. (New) The hypocholesteremic preparation according to claim 23, wherein the carboxylic acid has from about 12 to about 18 carbon atoms.--

--26. (New) The hypocholesteremic preparation according to claim 24, wherein the carboxylic acid has from about 12 to about 18 carbon atoms.--

--27. (New) The hypocholesteremic preparation according to claim 21, wherein the at least one component (b) comprises conjugated linoleic acid.--

--28. (New) The hypocholesteremic preparation according to claim 21, wherein the preparation is encapsulated in gelatin, in order to form a gelatin capsule.--

--29. (New) The hypocholesteremic preparation according to claim 28, wherein the at least one component (a) and the at least one component (b) are each independently present in an amount of from about 0.1 to about 50% by weight, based on the total weight of the gelatin capsule.--

--30. (New) The hypocholesteremic preparation according to claim 21, wherein the hypocholesteremic preparation is combined with a foodstuff.--

Please cancel claims 1-10, without prejudice.

REMARKS

Claims 11-30 are currently pending in the instant application.

The Specification has been amended to include the preferred section headings pursuant to 37 C.F.R. §1.77. An Abstract of the Disclosure has been added on a separate sheet following the claims. It is submitted that the amendments to the Specification made herein introduce no new matter. Their entry is therefore proper and respectfully requested.

Original claims 1-10 have been canceled and replaced with new claims 11-30 in order to remove multiple dependencies and to place the claims in more proper U.S. format for examination. New claims 11-30 are supported by the claims as originally filed and in the Specification, for example, at page 2, line 17, through page 4, line 22; at page 7, line 36, through page 8, line 13; and in the Examples. No new matter has been introduced. Entry is therefore proper and respectfully requested.

Prompt examination of the instant application in view of the amendments made herein is respectfully requested.

Respectfully submitted,

BERND FABRY

May 15, 2000
(Date)

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ABSTRACT OF THE DISCLOSURE

A hypocholesteremic preparation containing at least one component (a) selected from the group consisting of phytostenols and phytostenol esters and at least one component (b) selected from conjugated fatty acids having from about 6 to about 24 carbon atoms and glycerides of conjugated fatty acids having from about 6 to about 24 carbon atoms is disclosed. Methods of reducing serum cholesterol content in a mammal via administration of hypocholesteremic preparations described herein are also disclosed.

"Express Mail" mailing label number EL541612068US .

PATENT
Docket No. H 3185 PCT/US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

RE: PCT/EP98/07059
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PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Box PCT
Washington, DC 20231

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--TITLE OF THE INVENTION

Hypocholesteremic Preparations Containing
Mixtures of Phytostenol(ester)s and Conjugated Fatty Acids,
and Methods of Reducing Serum Cholesterol Levels Using the Same

USE OF MIXTURES OF ACTIVE AGENTS CONTAINING PHYTOSTENOL FOR PRODUCING HYPOCHOLESTEREMIC PREPARATIONS

Field of the invention

The invention relates to the use of synergistic mixtures of phytostenols or phytostenol esters and conjugated fatty acids for producing preparations for decreasing the cholesterol content in the serum of warm-blooded animals.

Prior art

Hypocholesteremic active agents are understood as meaning preparations which lead to a decrease in the cholesterol content in the serum of warm-blooded animals without an inhibition or lowering of the formation of cholesterol in the blood occurring. Phytostenols, i.e. plant stenols, and their esters with fatty acids have already been proposed for this purpose by Peterson et al. in **J. Nutrit. 50, 191 (1953).** The Patent Specifications **US 3,089,939, US 3,203,862** as well as the German Laid-Open Specification **DE-A 2035069** (Procter & Gamble) also point in the same direction. The active agents are customarily added to cooking or food oils and then ingested via the food, the amounts employed, however, as a rule being low and customarily below 0.5% by weight in order to prevent the food oils from becoming cloudy or the stenols from being precipitated on addition of water. For use in the foodstuffs area, in cosmetics, pharmaceutical preparations and in the agrarian sector, storage-stable emulsions of the stenol esters in sugar or polyglycerol esters are proposed in European Patent Application **EP-A1 0289636** (Ashai). The incorporation of sitostanol esters to decrease the blood cholesterol content in margarine, butter, mayonnaise, salad dressings and the

like is proposed in European Patent Specification EP-B1 0594612 (Raision).

The disadvantage, however, is that the phytostenol esters can customarily be added to the foodstuffs only in small amounts, as otherwise there is the danger that they will impair the taste and/or the consistency of the preparations. For a lasting effect on the cholesterol content in the blood, however, the intake of larger amounts of phytostenols or phytostenol esters would be desirable. Furthermore, the rate at which the substances decrease the content of cholesterol in the serum is worthy of improvement. The object of the invention consequently consisted in remedying these deficiencies.

Description of the invention

The invention relates to the use of mixtures of active agents for producing hypocholesteremic preparations with the proviso that

(a) phytostenols and/or phytostenol esters and
(b) fatty acids having 6 to 24 carbon atoms and at least two conjugated double bonds or their glycerides

are employed.

Surprisingly, it has been found that mixtures of phytostenols or phytostenol esters with conjugated fatty acids or fatty acid glycerides synergistically cause the reduction of the cholesterol content in the blood serum. Encapsulated in gelatin or directly added to foodstuffs, both the mixtures of active agents can be taken orally without problems.

Phytostenols and phytostenol esters

Phytostenols (or synonymously phytosterols) are understood as meaning plant steroids which carry a hydroxyl group only on C-3, but otherwise no functional groups. As a rule, the phytostenols have 27 to 30 carbon atoms and a double bond in the 5/6, optionally 7/8, 8/9 or other positions. In addition to these unsatura-

ted species, suitable stenols are also the saturated compounds obtainable by hardening, which are designated stanols and are additionally included by the present invention. Typical examples of suitable phytostenols are, for example, ergostenols, campestenols, stigmastenols, brassica stenols, and preferably sitostenols or sitostanols and in particular β-sitostenols or β-sitostanols. In addition to the phytostenols mentioned, their esters are preferably employed. The acid component of the ester can have its origin in carboxylic acids of the formula (I)

R^1CO-OH (I)

in which R^1CO is an aliphatic, linear or branched acyl radical having 2 to 22 carbon atoms and 0 and/or 1, 2 or 3 double bonds. Typical examples are acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, caprylic acid, 2-ethylhexanoic acid, capric acid, lauric acid, isotridecanoic acid, myristic acid, palmitic acid, palmitoleic acid, stearic acid, isostearic acid, oleic acid, elaidic acid, petroselinic acid, linoleic acid, linolenic acid, elaeostearic acid, arachic acid, gadoleic acid, behenic acid and erucic acid, and their technical mixtures, which are obtained, for example, in the pressure cracking of natural fats and oils, in the reduction of aldehydes from Roelen's oxo synthesis or the dimerization of unsaturated fatty acids. Preferred technical fatty acids are those having 12 to 18 carbon atoms such as, for example, coconut, palmitic, palm kernel or tallow fatty acid. The use of esters of β-sitostenol or β-sitostanol with fatty acids having 12 to 18 carbon atoms is particularly preferred. These esters can be produced both by direct esterification of the phytostenols with the fatty acids or else by transesterification with fatty acid lower alkyl esters or triglycerides in the presence of suitable catalysts, such as, for example, sodium ethylate or especially also enzymes [cf. EP-A2 0195311

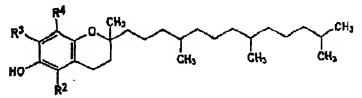
(Yoshikawa)]. The hypocholesteremic action of phytostenols or phytostenol esters is disclosed, for example, in European Patent Specification **EP-B1 0594612** (Raision) and the literature cited therein.

Conjugated fatty acids

The term conjugated fatty acids is understood as meaning aliphatic carboxylic acids having 6 to 24, preferably 16 to 18, carbon atoms and at least two double bonds which are conjugated to one another, i.e. are separated by exactly one single bond. Typical examples are the conjugated linoleic acid (CLA) or conjugated fish fatty acids. It is known of conjugated linoleic acid that it has a low hypocholesteremic action; its use in foodstuffs or as a foodstuff supplement, however, is attributed to the fact that it assists the combustion of endogenous fats [cf. **EP-B1 0579901**, **WO 94/16690**, **WO 96/06605**; (WARF)]. Instead of the conjugated fatty acids, the corresponding full or partial esters with glycerol can also be employed for reasons of taste and because of the better fat solubility.

Tocopherols

The mixtures of active agents may contain potentiating agents of the tocopherols type as further constituents. Tocopherols are understood as meaning chroman-6-ols (3,4-dihydro-2-*H*-1benzopyran-6-ols) substituted in the 2-position by 4,8,12-trimethyltridecyl radicals, which obey the formula (II)



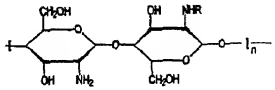
(II)

in which R^2, R^3 and R^4 independently of one another are hydrogen or a methyl group. Tocopherols belong to the

bioquinones, i.e. polyprenylated 1,4-benzo- or naphthoquinones whose prenyl chains are saturated to a greater or lesser extent. Typical examples of tocopherols which are possible within the meaning of the invention as component (b) are ubiquinones, boviquinones, K vitamins and/or menaquinones (2-methyl-1,4-naphthoquinones). In the case of the tocopherols, a differentiation is furthermore made between α, β, γ-, δ- and ε-tocopherols, where the latter can still have the original unsaturated prenyl side chain, and α-tocopherolquinone and -hydroquinone, in which the pyran ring system is opened. Preferably, as component (b), α-tocopherol (vitamin E) of the formula (II) is employed, in which R^2, R^3 and R^4 are methyl groups, or esters of α-tocopherol with carboxylic acids having 2 to 22 carbon atoms, such as, for example, α-tocopherol acetate or α-tocopherol palmitate.

Chitosans

As further constituents, the mixtures of active agents can contain potentiating preparations of the chitosans type. Chitosans are biopolymers and are included in the hydrocolloids group. Considered chemically, they are partially deacetylated chitins of different molecular weights, which contain the following - idealized - monomer unit (III)



(III)

In contrast to most hydrocolloids, which are negatively charged in the biological pH region, chitosans are cationic biopolymers under these conditions. The positively charged chitosans can interact with oppositely charged surfaces and are therefore employed in cosmetic hair- and body-care preparations and

pharmaceutical preparations (cf. **Ullmann's Encyclopedia of Industrial Chemistry, 5th Ed., Vol. A6, Weinheim, Verlag Chemie, 1986, pp. 231-332**). Overviews on this subject have also appeared, for example, by B. Gesslein et al. in **HAPPI 27, 57 (1990)**, O. Skaugrud in **Drug Cosm. Ind. 148, 24 (1991)** and E. Onsoyen et al. in **Seifen-Öle-Fette-Wachse 117, 633 (1991)**. To produce chitosans, chitin, preferably the shell remains from crustaceans, which are available in large amounts as cheap raw materials, is used as a starting material. In a process which has been described for the first time by Hackmann et al., the chitin is customarily first deproteinated by addition of bases, demineralized by addition of mineral acids and finally deacetylated by addition of strong bases, it being possible for the molecular weights to be distributed over a wide spectrum. Corresponding processes are known, for example, from **Makromol. Chem. 177, 3589 (1976)** or French Patent Application **FR-A 2701266**. In a preferred embodiment of the invention, a chitin degradation product, as is described in International Patent Application **WO 96/16991** (Henkel), or its degradation product with hydrogen peroxide is employed.

Phytostenol sulfates

The mixtures of active agents can contain potentiating preparations of the phytostenol sulfates type as further constituents. Phytostenol sulfates are known substances which can be prepared, for example, by sulfation of phytostenols with a complex of sulfur trioxide and pyridine in benzene [cf. **J. Am. Chem. Soc. 63, 1259 (1941)**]. Typical examples are the sulfates of ergostenols, campestenols, stigmastenols and sitostenols. The phytostenol sulfates can be present as alkali metal and/or alkaline earth metal salts, as ammonium, alkylammonium, alkanolammonium and/or glucammonium salts. As a rule, they are employed in the form of their sodium salts.

(Deoxy)ribonucleic acids

The mixtures of active agents can finally contain potentiating preparations of the (deoxy)ribonucleic acids type as further constituents. (Deoxy)-ribonucleic acids (DNA or RNA) are understood as meaning high molecular weight, threadlike polynucleotides which are derived from 2'-deoxy-β-D-ribonucleosides or D-ribonucleosides, which for their part in turn are synthesized from equivalent amounts of a nucleobase and the pentose 2-deoxy-D-ribofuranose or D-ribofuranose. As nucleobases, the DNA or RNA can contain the purine derivatives adenine and guanine and also the pyrimidines cytosine and thymine or uracil. In the nucleic acids, the nucleobases are linked N-glycosidically with carbon atom 1 of the ribose, adenosines, guanosines, cytidines and thymidines being formed in the individual case. In the acids, a phosphate group links the 5'-hydroxyl group of the nucleosides with the 3'-OH group of the following nucleoside in each case by means of a phosphodiester bridge with formation of single-stranded DNA or RNA. Because of the large ratio of length to diameter, DNA and RNA molecules are prone, even on mechanical stress, for example during extraction, to strand breakage. For this reason, the molecular weight of the nucleic acids can reach 10^3 to 10^9 daltons. Within the meaning of the invention, concentrated DNA and RNA solutions are employed, which are distinguished by a liquid-crystalline behavior. Preferably, deoxy- and ribonucleic acids are employed which are obtained from marine sources, for example by extraction of fish sperm, and which have a molecular weight in the region from 40,000 to 1,000,000 daltons.

Commercial applicability

The mixtures of active agents of the invention can contain the phytostenols and/or phytostenol esters and the conjugated fatty acids in the weight ratio 99:1 to 1:99, preferably 90:10 to 10:90, in particular 75:25

to 25:75 and particularly preferably 60:40 to 40:60. In a particular embodiment of the invention, the mixtures of active agents are encapsulated in gelatin in a manner known per se, components (a) and (b) in each case being employed in amounts from 0.1 to 50, preferably 1 to 30, in particular 5 to 25 and particularly preferably 10 to 15, % by weight - based on the weight of the gelatin capsules. In addition, it is possible to dissolve or to disperse the mixtures in customary foodstuffs, such as, for example: butter, margarine, dietetic food, deep-frying oils, food oils, mayonnaises, salad dressings, cocoa products, sausage and the like.

Examples

Examples 1 to 5, Comparative Examples C1 to C5

Gelatin capsules (weight about 1.5 g) having a content of 5 or 10% by weight of β-sitostenol or β-sitostenol ester and, if appropriate 5 or 10% by weight of conjugated linoleic acid (CLA) and also 0.5% by weight of radiolabeled cholesterol were prepared. To investigate the hypocholesteremic action, male rats (individual weight about 200 g) were allowed to fast overnight. The following day, a comminuted gelatin capsule was introduced into the experimental animals in each case with some salt-containing water by means of a stomach tube. After 3, 6, 12, 24 and 48 h, blood was taken from the animals and the content of radioactive cholesterol was determined. The results, which represent the mean value of the measurements of 10 experimental animals, are summarized in Table 1. The details on the decrease in the radioactivity are in each case interpreted with respect to a blind group of experimental animals, to which only gelatin capsules having a content of 20% by weight of vitamin E and an appropriate amount of radiolabeled cholesterol had been administered. The mixtures 1 to 5 are according to the invention; the mixtures C1 to C5 serve for comparison.

Table 1

Hypocholesteremic action (quantitative data as % by weight based on gelatin capsule)

Composition	1	2	3	4	5	C1	C2	C3	C4	C5
β-Sitostenol	5	–	–	–	–	10	–	–	–	–
β-Sitostanol	–	5	–	–	–	–	10	–	–	–
Lauric acid β-sitostenol ester	–	–	5	–	–	–	–	10	–	–
Lauric acid β-sitostanol ester	–	–	–	5	10	–	–	–	10	–
Conjugated linoleic acid	5	5	5	5	5	–	–	–	–	10
Radioactivity [% rel]										
- after 3 h	93	93	93	93	93	93	93	93	93	98
- after 6 h	84	83	83	83	81	87	86	87	86	91
- after 12 h	75	75	75	74	71	79	79	78	78	87
- after 24 h	54	51	47	45	40	62	60	59	69	75
- after 48 h	23	21	22	19	12	35	32	35	32	60

The examples show the synergistic decrease in the cholesterol content in the blood when using mixtures of the stenols or stenol esters with CLA.

Patent Claims

1. The use of mixtures of active agents for producing hypocholesteremic preparations, **which comprises** employing

(a) phytostenols and/or phytostenol esters and

(b) fatty acids having 6 to 24 carbon atoms and at least two conjugated double bonds or their glycerides.

2. The use as claimed in claim 1, **wherein**, as component (a), β-sitostenol, β-sitostanol or its ester is employed.

3. The use as claimed in claims 1 and 2, **wherein**, as component (a), esters of β-sitostenol or β-sitostanol with carboxylic acids of the formula (I) are employed

R^1CO-OH (I)

in which R^1CO is an aliphatic, linear or branched acyl radical having 2 to 22 carbon atoms and 0 and/or 1, 2 or 3 double bonds.

4. The use as claimed in claims 1 to 3, **wherein**, as component (a), esters of β-sitostenol or β-sitostanol with fatty acids having 12 to 18 carbon atoms are employed.

5. The use as claimed in claims 1 to 4, **wherein**, as component (b), conjugated linoleic acid (CLA) is employed.

6. The use as claimed in claims 1 to 5, **wherein** components (a) and (b) are employed in the weight ratio 99:1 to 1:99.

7. The use as claimed in claims 1 to 6, **wherein** components (a) and (b) are encapsulated in gelatin.

8. The use as claimed in claim 7, **wherein** components (a) and (b) are in each case employed in

amounts from 0.1 to 50% by weight - based on the weight of the gelatin capsules.

9. The use as claimed in claims 1 to 6, **wherein** components (a) and (b) are added to foodstuffs.

10. The use as claimed in claim 1, **wherein** components (a) and (b) are dispersed in butter, margarine, dietetic food, deep-frying oils, food oils, mayonnaises, salad dressings, cocoa products, sausage and the like.

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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION

☐ Declaration Submitted with Initial Filing OR ☒ Declaration Submitted after Initial Filing

Attorney Docket Number	H 3185 PCT/US
First Named Inventor	FABRY, Bernd
COMPLETE IF KNOWN	
Application Number	09/554,387
Filing Date	06/29/2000
Group Art Unit	
Examiner Name	

As a below named inventor, I hereby declare that:
My residence, post office address, and citizenship are as stated below next to my name.
I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

USE OF MIXTURES OF ACTIVE AGENTS CONTAINING PHYTOSTENOL FOR PRODUCING HYPOCHOLESTERAEMIC PREPARATIONS

(Title of the Invention)

the specification of which
☐ is attached hereto
OR
☒ was filed on (MM/DD/YYYY) 11/05/1998 as United States Application Number or PCT International Application Number PCT/EP98/07059 and was amended on (MM/DD/YYYY) _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37 Code of Federal Regulations, § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY	Priority Not Claimed	Certified Copy Attached? YES	Certified Copy Attached? NO
197 50 453.1	Germany	11/14/1997	☐	☐	☒

☐ Additional foreign application numbers are listed on a supplemental priority sheet attached hereto:

I hereby claim the benefit under Title 35, United States Code §119(e) of any United States provisional application(s) listed below.

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U.S. Parent Application Number	PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number *(if applicable)*
	PCT/EP98/07059	11/05/1998	

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Name of Sole or First Inventor: [ ] A petition has been filed for this unsigned

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